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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/341,894	Applicant(s) Plechaczyk et al.
	Examiner P ter Brunovskis	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Sep 28, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 3-8, 11-15, and 20-31* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-8, 11-15, and 20-31* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The response filed 9/28/00 has been entered as well as newly amended claims 1, 3-8, 11-14, and 20. Cancellation of claims 2, 9-19, and 15-19 is acknowledged. Claims 1, 3-8, 11-14, and 20 are pending in the instant application. Applicant's arguments filed 9/28/00 will only be considered to the extent that they apply to newly amended claims; arguments directed to any other subject matter is considered moot.

Claim Objections

Claim 26, 27, 29, and 30 are objected to because of the following informalities: In line 3 of claim 26 the word "an" between "and" and "another" should be deleted; in line 4 of steps (a) and (b) and line 5 of step (c) "fragment" should be changed to --fragments--. In claim 27, *the second* "fragment" in line 3 should be changed to --fragments-- . In claims 27 and 30, "(IRES sequence)" should either be deleted or changed to --(IRES)--. In claim 29, "of antibody molecule from" should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-8, 11-15, and 20-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 20 (and dependent claims) are indefinite in their recitation of the term "unmodified antibody polypeptide" since it is not clear how this term is defined, what its metes and bounds are, or what is meant by "unmodified" in this context. Moroever, it is unclear how an "unmodified antibody polypeptide" can be a "functional fragment thereof", since a "fragment thereof" would appear, by definition, to consist of a *modified* antibody polypeptide or fragment. The claims are also indefinite in their recitation of the term "a heavy chain" since it is not clear whether the antibody polypeptide is considered "heavy" or whether "heavy chain" is intended to convey "immunoglobulin heavy chain". The claims are also indefinite in their recitation of the functional limitation "does not induce an immune response..." in step (ii), since it is unclear what context applies to "induc[tion] [of] an immune response"--e.g. immune response in what? species of the host animal? In addition, the claims are indefinite in their recitation of the phrase "wherein the coding polypeptide is operably linked to..." in steps (iii) and (iv) because it is not clear how a *polypeptide* can be operably linked to a "promoter" (contained in a polynucleotide) or a "polynucleotide element". Further, claim 1 is indefinite in its recitation of step (b) since it is unclear how *method step* (b) relates back to the preamble reciting "[t]he cell of claim 21" or whether the claim is in fact draw to a composition or a method of using said composition. Similarly, claim 20 is indefinite because it is unclear how method steps (2) and (3) reciting the

additional steps of culturing cells and introducing them into a host mammal relate back to "[a] method of making a mammalian non-plasmocyte cell comprising..."; thus it is unclear whether claim 20 is drawn to a method of making cells or a method of using cells.

Claims 1 and 20 (and dependent claims) recite the limitation "the coding polypeptide" in steps (iii) and (iv) of the rejected claims. There is insufficient antecedent basis for this limitation in the claims and it's unclear what the limitation means.

Claim 3 is indefinite in its recitation of the phrase "wherein the nucleic acid is associated with or complexed to with a carrier substance" because it is unclear what is meant by "carrier substance" in the context *a cell containing a nucleic acid.* It would appear that a nucleic acid within a cell is not subject to control of the artisan, hence it is not clear how an artisan would control an association or complexation of a nucleic acid therein with a "carrier substance", nor is it clear how the substance is a "carrier" in this context (i.e. carrier how-in what way, for what?).

Claim 6 (and dependent claims) is indefinite in its recitation of method steps which do not relate back to the preamble reciting "[t]he cell of claim 21". It is unclear whether the claim is intended to be drawn to a composition or a method.

Claims 6-8 are indefinite in their recitation of the term "the host mammal" since the base claim (i.e. cl. 21) merely recites "host mammal" as an intended use limitation whereas the rejected claims recite "the host mammal" as an inherent and essential claim limitation.

Claim 15 is indefinite in its recitation of the term "pharmaceutically acceptable vehicle" within the context of *cells*. Although this term is described in the context of nucleic acids for

local injection or electroporation (e.g. p. 6, lines 2-6) it is not clear what is meant by this term in the context of *cells*.

Claim 20 is indefinite in its recitation of the term "transferring" since it is not clear what is meant by this term, nor is it clear "from what to what" is the nucleic acid transferr[ed]". Changing the term "transferring" to --transfecting-- would obviate the problem.

Claims 21, 25, 26, 29, and 31 (and dependent claims) are indefinite in their recitation of the term "operably linked" in: line 2 of step (b) in claims 21 and 25 and line 2 of step (c) in claims 26, 29, and 31. As presently recited it is unclear whether this term is directed to the "signal peptide" or the "nucleotide sequence coding for...". If directed to "signal peptide", it is unclear how the *nucleotide* sequence is operably linked to a *peptide* sequence.

Claim 22 is indefinite in its recitation of the term "complete antibody" since it is unclear how this term is defined or what its metes and bounds are.

Claims 22, 24, and 28 are indefinite because it is unclear what is meant by "single" in the context of "single antibody heavy (or light) chain"--e.g. whether the cell expressing only one chain or the other etc.

Claim 23 recites the limitation "the antibody molecule fragment" in line 1 of step (a). There is insufficient antecedent basis for this limitation in the claim.

Claims 24 and 28 are indefinite in their recitation of the term "each of" in line 1, since it is unclear whether by "each" it is meant that *both* antibody molecules are selected from the *same*

class of antibody fragments (e.g. *both* from light chain) or whether one is selected from class and the other is selected from another class (e.g. one from light chain and one from heavy chain).

Claim 25 is indefinite in its recitation of the phrase "the heavy and light chains of an antibody molecule" in step (a) since there is nothing in the preceding section that suggesting that the heavy and light chains are from *the same antibody molecule*. Therefore, it is not clear whether the claim intends to recite a heavy and light chain from the same antibody or whether "an antibody molecule" in line 3 of step (a) merely expresses the product of two independent chains forming a molecule (e.g. chimeric molecule etc.).

Claim 25 recites the limitation "the heavy and light chain antibody molecules" in lines 3-4 of step (b). There is insufficient antecedent basis for this limitation in the claim.

Claim 26 (and dependent claims) recites the limitation "said first and second nucleotide sequences" in line 1 of steps (a) and (b). There is insufficient antecedent basis for this limitation in the claim.

Claims 26 and 29 (and dependent claims) recite the limitations, "the most downstream nucleotide sequence" in line 2 of step (a); and "the same polycistronic RNA" in line 4 of steps (a) and (b) and line 5 of step (c). There is insufficient antecedent basis for these limitations in the claims.

Claims 26 and 29 (and dependent claims) is constructed in a confusing and somewhat redundant manner and is indefinite in its recitation of the phrase "separated by a nucleotide sequence permitting translation of the most downstream nucleotide sequence..." in steps (a), (b),

and (c), since it is unclear what the nature of the [intervening] sequence is or how it is used "for translation of *both* antibody molecule fragment[s] from the same...RNA" (emphasis added). The term "permitting" merely means not preventing; therefore, it is unclear how the [intervening] sequence is defined or what its metes and bounds are. Further, the claims are indefinite in their recitation of the phrase "are operably linked to the same promoter" in step (b), since the confusing construction of this step does not make clear what components are actually "operably linked". Simplifying the construction of these claims to remove redundancy and a more accurately defining the relationships between specific nucleotide sequences and/or RNA elements would obviate these problems.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 11-15, and 20-31 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

All of the instant claims recite "a nucleotide sequence element coding for a signal peptide operably linked to the nucleotide sequence coding for the antibody molecule fragment". However, there is no mention of signal peptides anywhere in the instant specification. In general, there is no nexus between many of the generic compositions and generic methods recited in the claims and their description in the specification. For example, the specification does not describe "unmodified antibody polypeptides" or cells of claim 21 comprising polynucleotides encoding an unmodified *heavy chain*, either by itself or wherein it "does not induce an immune response sufficient for neutralizing the antibody polypeptide". In Applicants response filed 9/28/00 it is argued that support for "wherein the antibody polypeptide does not induce an immune response neutralizing the antibody polypeptide" (p. 14) is provided in the specification at pg. 16, lines 13-14. However, this assertion is not persuasive, since the recited passage is only described in the context of "expressing a stable Tg10 monoclonal antibody after retroviral transduction implanted at the level of the *tibialis anterior* of the C3H mouse". There is no evidence of record that Applicants contemplated this limitation in the context of the broad generic compositions or generic methods recited in claims 1 and 20, to which the limitation depends, nor is there any established nexus between the two.

Additionally, the specification does not provide proper written description for the terms "complete antibody" (cl. 22), "single antibody light (or heavy) chain" (cl. 22, 24, 28), "sequences permitting translation of the most downstream nucleotide sequence" (cl. 26, 29), "polycistronic RNA" (cl. 26, 29), or "IRES sequence" (cl. 27, 30), particularly in the context of the claimed

subject matter. The response contends that support for "the recitation of --a single antibody chain-- and --a single antibody heavy chain-- is found in the specification at pg. 12, lines 9 and 20. However, the only support provided on pg. 12 is perhaps for incorporation of the heavy and light chains of antibody Tg10 is in the context of a retroviral vectors. There is no evidence of record that Applicants contemplated this limitation in the broader context of the generic compositions recited in claims 21, 23, or 26, to which the limitation depends, nor is there any established nexus between the two.

The response further contends that "[s]upport for --IRES sequence-- is found in the specification at pg. 13, line 5. However, there is no such recitation indicated; although pg. 12 does mention use of an IRES sequence, it is only in the context of vector *species* comprising cDNAs of the light and heavy chains of antibody Tg10 (i.e. PM130, PM117, and PM124). There is no evidence of record that Applicants contemplated this limitation in the broader context of the generic compositions recited in claims 26, 27, 29, and 30, to which the limitation depends, nor is there any established nexus between the two.

Further, the specification does not provide any written description of non-plasmocyte cells genetically modified *with two distinct nucleic acids*, as recited in claims 23-25. The response contends that support for recitation of "two distinct nucleic acid[s]" is found in the specification at pg. 13, TABLE 1. However, this contention is not supported by the evidence of record since TABLE 1 only refers to a particular *species* of embodiment comprising two distinct nucleic acids, as recited in claims 23 and 25. There is no evidence of record that Applicants contemplated this

limitation in the broader context of the generic compositions recited in claims 23-25, to which the limitation depends, nor is there any established nexus between the two.

Additionally, the specification does not provide any written description for non-plasmocyte cells genetically modified with a nucleic acid comprising one nucleotide sequence coding for one fragment or chain (i.e. heavy or light) of an antibody molecule and another nucleotide sequence coding for another, as recited in claims 26-30. Applicants contend that "[s]upport for --with a nucleic acid, wherein the nucleic acid comprises one nucleotide sequence coding for one fragment of an antibody molecule and an another nucleotide sequence coding for another fragment of an antibody molecule-- in claims 26 and 29 is found in the specification, pg. 13, lines 1-2 (pLXPXSN)". However, this contention is not supported by the evidence of record, since pg. 13, lines 1-2 fails to describe any such embodiment. Although pLXPXSN is described on pg. 12, line 24, the recitation therein only refers to a particular *species* of embodiment comprising one nucleotide sequence coding for one fragment of an antibody molecule and another nucleotide sequence coding for another fragment of an antibody molecule. There is no evidence of record that Applicants contemplated this limitation in the broader context of the generic compositions recited in claims 26-30, to which the limitation depends, nor is there any established nexus between the two. A single species does not an provide written description or evidence for possession for any and all arbitrary genera into which, in hindsight, it may fall.

Claims 1, 3-8, 11-15, and 20-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To the extent that the rejected claims contain new matter that does not meet the written description requirement as described above, the rejected claims are not enabled, since the specification cannot teach how to make or use embodiments that have not been described.

Claims 1, 6, 20, and 31 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth against prior claims 1-20 in the Office Action of 3/29/00 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To the extent that claims 1, 6, 20, and 31 embrace implantation of genetically modified non-plasmocyte cells in a host mammal, they are interpreted as being drawn to ex vivo gene therapy, since the specification does not describe any other non-therapeutic use. Further, for the reasons of record set forth in the previous enablement rejection against ex vivo claims, the newly amended claims fail to overcome the prima facie case against enablement. Applicant's arguments filed 9/28/00 have been fully considered but they are not persuasive. The response contends that "[t]he graft of the ex vivo genetically modified cells as disclosed by the specification constitutes a good demonstration". However, it is not clear in what way the sole ex vivo working example

constitutes a "good demonstration" of anything other than perhaps an ability to secrete antibodies from implanted C2C12 cells in a syngeneic C3H mice, for purposes that are not entirely clear. Further, the specification fails to overcome the problems previously set forth in regard to engraftment of myoblast cells in humans.

Nature of the invention and state of the prior art.

The specification does not disclose any non-therapeutic use for such implantation in syngeneic mice; therefore, the argument that "[b]y contrast, the approach disclosed by the Applicants involves the transfer of particular genes to particular cells, allowing the expression and secretion of proteins encoded by those genes" (p. 19) is moot.

The fact that "gene therapy has developed considerably since 1998" bears no probative value in the instant case, insofar as the specification must provide a disclosure commensurate with enablement *at the time the invention was made.* Recent successes in the art are only probative to the extent that they employ methodologies and treatments that are *fully described* in the instant application. The fact that "human myoblast grafts are currently being attempted" has no probative value, since the instant specification does provide guidance on how to overcome the previous problems known in the art which were briefly summarized in the previous Office Action of 3/29/00. In addition, there is no evidence of record that Applicants contemplated the compositions or methods of instant invention for purposes of optimizing gene therapy protocols as suggested in the response (bottom of p. 19), nor does the specification provide sufficient

guidance on how to optimize such protocols using the compositions or methods of instant invention.

Breadth of claims

The newly amended claims are extremely broad and recite new matter not described in the instant specification. For example, the newly amended claims recite cells genetically modified to secrete antibody polypeptides that do not induce an immune response sufficient for neutralizing the antibody polypeptide. However, the specification provides no guidance teaching how to design such antibodies to meet this limitation, especially when the antibody contains non-endogenous epitopes. There is no guidance for example teaching how to "humanize" antibodies so that they do not induce an immune response. Applicants contend their invention concerns a *new* antibody delivery system. However, this view is not supported by the prior art of record (see 35 U.S.C. 102 and 103 rejections below).

Predictability of the art

Applicants arguments are moot in view of their failure to describe any substantial or well-established use for secretion of the antibodies of the claimed invention apart from ex vivo gene therapy which is clearly unpredictable, insofar as it was not routinely performed at the time the

Guidance and working examples

Applicants arguments concerning the utility of monoclonal antibodies is moot in view of the subject matter to which the invention is drawn. There is a vast difference between injecting

recombinant monoclonal antibodies and implanting recombinant cells secreting therapeutic levels of such. The anti-Tg10 working example merely demonstrates production of an antibody in the serum of syngeneic mice from implanted C2C12 cells. The specification, however, fails to provide a nexus between this type of implantation and the broad scope of implantations in humans, for example, using e.g. the broad scope of cells recited in claim 11.

The response further contends that the specification *does* provide sufficient guidance teaching "how to make embodiments guaranteeing the expression in vivo of an antibody gene and the secretion in the blood circulation of a mammal". However, in view of the new matter in the newly amended claims which is not described in the specification, this problem is even greater than before. It is argued that "the first 20 amino acids, from position -20 to position -1, correspond to the signal peptide coding for the heavy chain signal peptide" and suggest that the use of an Internal Ribosomal Entry Sequence (IRES) is provided to "implement the in vivo expression of antibody genes" (p. 21). However, none of the signal peptide information is described in the specification, nor is there any nexus provided between this or the IRES teachings particularly with respect to the broad range of cell embodiments recited in the rejected claims.

With regard to the arguments concerning concentration of therapeutic antibody levels (p. 21), the response relies on teachings (e.g. changing the promoter, changing the gene delivery system [adenoviral?], or implanting higher number of cells) requiring guidance or written description that is not sufficiently covered in the specification to be enabled. In the absence of a substantial or well-established use, verification of antibody production (i.e. Tg10) in mice does

not carry sufficient probative value for overcoming the prima facie case against enablement. The fact that "[m]any laboratories are actually working with this approach" of extrapolating in humans the results obtained in mice involving implantation of antibody-secreting myotubes is consistent with the fact that no one was able to successfully able to get this procedure to work in humans at the time the invention was made or at the present time.

Given the unpredictable and undeveloped state of the art as described above, it would require undue experimentation for one skilled in the art to appropriately develop the claimed invention for treating any disease by ex vivo gene therapy. This is particularly true given the state of the art, the nature of the invention, the unpredictability of the art, the scarcity of guidance and working examples in the specification, and the amount of experimentation necessary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Note: In claims 1, 6, and 20 the "for use" limitations merely recite an intended use and carry no patentable weight for purposes of applying prior art.

Claims 4, 12, 13, and 21-25 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Wright et al. (Crit. Rev. Immunol., 12(3,4):125-168, 1992).

Wright et al. reviews and discloses non-plasmocyte cells genetically modified with nucleic acids capable of secreting antibodies (e.g. anti-CEA tumor cell antigen) into the bloodstream of mammals (see pp. 130-131, section 6., "Nonlymphoid cell expression"). Wright also discloses vectors and methods for generating various chimeric antibodies, including single-chain antibodies, inherently comprising nucleotide sequences coding for immunoglobulin heavy and light chains that are operably linked to promoters and signal sequences for secreting said antibodies (p. 149-151, section B., "Single-chain Fvs" etc.).

Applicants contend that Wright does not disclose the claimed invention because Wright does not disclose "each element of the claim under consideration" (p. 23) and because Wright's disclosure neither discloses a method for the production of monoclonal antibodies in vivo, nor secretion in mammals from non-B cells of said antibodies. These arguments are not persuasive because they rely on features (i.e., in vivo production of antibodies etc.) that are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). With regard to the requirement that the reference requires "each element of the claim under consideration" be disclosed, it is not clear from the response what "element[s]" Applicants refer to. If it is those elements set forth in the subsequent paragraphs as set forth above, the argument is moot in view of the fact that the rejected claims do not rely on said elements or features.

Claims 4, 11-13, 21-26, 28, and 29 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Stevenson et al. (Ann. N.Y. Acad. Sci., 772:212-226, 1995).

Stevenson et al. disclose injection in a mammal of a nucleic acid vector capable of secreting in the blood circulation of a mouse a chimeric antibody directed against a tumor cell antigen. Further, Stevenson discloses intramuscular injection of a nucleic acid resulting in production of non-plasmocyte cells genetically-modified with said nucleic acid (see p. 215, middle of page). Since the scFv-based nucleic acid comprises two distinct nucleic acids, one coding for one fragment of the heavy chain variable region and the other coding for another region of the light chain variable region, the disclosure meets the limitations recited in claims 23 and 29. Further, since the nucleic acid coding for the linked chains in the chimeric scFv antibody molecule comprises nucleotide sequences operatively linked to a RSV LTR promoter and a nucleotide sequence element coding for a human V_H1 signal peptide, it would also meet the limitations of claim. Additionally, since the nucleotide sequence is separated by a nucleotide sequence permitting (i.e. not preventing) translation of the most downstream nucleotide sequence coding for...(i.e. linker sequence, see Fig. 2, p. 216), the disclosure meets the limitations recited in claims 26 and 29.

Applicants contend that Stevenson does not anticipate the pending claims because Stevenson discloses a vaccine approach involving injection of vector as opposed to implantation of cells. However, this argument is non-persuasive because it relies on features (i.e., implantation of cells etc.) that are not recited in the rejected claim(s). Although the claims are interpreted in

light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 4, 5, 11-13, 21-26, 28, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Moritz et al. (Proc. Natl. Acad. Sci. USA, 91:4318-4322, 1994).

Moritz discloses mammalian non-plasmocyte cells (i.e. cytotoxic T-lymphocytes) genetically modified with nucleic acids coding for a chimeric antibody molecule produced by in vivo gene transfer of using a viral vector (pLXSN retroviral system) encoding a nucleotide sequence coding for a chimeric antibody molecule directed against a tumor cell antigen wherein said sequence is operatively linked to a promoter and a nucleotide sequence element coding for a signal peptide. Whether or not the signal peptide is in fact operational for secretion of the disclosed construction is immaterial to whether the disclosure constitutes prior art since the "for secreting" limitation is an intended use which is given no patentable weight. Since the scFv-based nucleic acid comprises two distinct nucleic acids, one coding for one fragment of the heavy chain variable region and the other coding for another region of the light chain variable region, the disclosure meets the limitations recited in claims 23 and 29. Further since each of the nucleotide sequences encoding the linked chains is operably linked to a RSV LTR promoter and a human V_H1 signal peptide, it would also meet the limitations of claim 25. Additionally, since the nucleotide sequence is separated by a nucleotide sequence permitting (i.e. not preventing)

translation of the most downstream nucleotide sequence coding for...(i.e. linker sequence, see Fig. 2, p. 4320), the disclosure meets the limitations recited in claims 26 and 29.

Applicants contend that Moritz does not anticipate the pending claims, that Moritz does not introduce the recombinant cells into a mammal, that cytotoxic T-lymphocytes are not "non-plasmocyte cells", and that Moritz does disclose a secreting antibody cell, nor a delivery method for antibodies reaching the blood circulation (p. 24-25). These arguments are not persuasive, primarily because they rely on features (i.e., implantation of cells, antibody-secreting cells, or antibodies reaching the blood circulation) that are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The argument that cytotoxic T-lymphocytes are not "non-plasmocyte cells" is not valid, since the *only* recitation of plasmocyte cells in the specification defines them as "cells specialized for antibody production" (p. 4, line 7).

Claims 4, 11, 12, 14, 21-26, 28, and 29 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chen et al. (Proc. Natl. Acad. Sci. USA, 91:5932-5936, 1994).

Chen et al. discloses mammalian non-plasmocyte cells (i.e. COS-1 and $CD4^+$ T-lymphocytes) genetically modified by transfection with a vector (i.e. pCMV-Fab105) coding for a Fab antibody molecule directed against a virus (i.e. HIV) for secretion of the recombinant antibodies into the blood circulation of mammals (see e.g. abstract). The vector in the transduced

cells comprises Fab-encoding nucleotide sequences operatively linked to promoters and nucleotide sequence elements encoding a signal peptide. Since the Fab-encoding vector comprises two distinct nucleic acids, one coding for one fragment of the heavy chain variable region and the other coding for another region of the light chain variable region, the disclosure meets the limitations recited in claims 23 and 29. Further since each of the nucleotide sequences encoding the linked chains is operably linked to a CMV promoter and a signal sequence (Fig. 1, p. 5932), it would also meet the limitations of claim 25. Additionally, since the nucleotide sequence is separated by a nucleotide sequence permitting (i.e. not preventing) translation of the most downstream nucleotide sequence coding for...(e.g. polyA sequence, etc.), the disclosure meets the limitations recited in claims 26 and 29.

Applicants contend that Chen does not anticipate the pending claims because Chen neither discloses introduction of recombinant cells in a mammal, nor secretion or diffusion of antibody fragments in the blood circulation and because the non-plasmocyte cells of the invention present a much longer-length half-life term than T lymphocytes. It should be noted that Applicants *do not* dispute T-lymphocytes as *not* being non-plasmocyte cells as in the case of Moritz above. More importantly, the arguments set forth in the response are not persuasive since primarily because they rely on features (i.e., implantation of cells, antibodies reaching the blood circulation, etc.) that are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants arguments concerning the references by Schlom and Schinstine (p. 25-26) are moot, since no rejection was set forth using these references. These references were merely provided to allow Applicants the opportunity to amend their prior claims around the prior art.

Claims 4, 5, 11, 12, 14, and 21-30 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chen et al. (Hum. Gene Ther., 7:1515-1525, 8/1996).

Chen et al. discloses mammalian non-plasmocyte cells (i.e. COS-1 and $CD4^+$ T-lymphocytes) genetically modified by transfection with a virus vector (i.e. pAAV-Fab105) coding for a Fab antibody molecule directed against a virus (i.e. HIV) for secretion of the recombinant antibodies into the blood circulation of mammals (see e.g. abstract). The vector in the transduced cells comprises Fab-encoding nucleotide sequences operatively linked to a promoter and nucleotide sequence elements encoding a signal peptide. Since the Fab-encoding vector comprises two distinct nucleic acids, one coding for one fragment of the heavy chain variable region and the other coding for another region of the light chain variable region, the disclosure meets the limitations recited in claims 23 and 29. Further, since each of the nucleotide sequences encoding the linked chains are operably linked to a CMV promoter and a signal sequence (Fig. 1, p. 1517), it would also meet the limitations of claim 25. Additionally, since the first and second nucleotide sequences are separated by a nucleotide sequence permitting translation of the most downstream nucleotide sequence coding for...(i.e. IRES), the disclosure meets the limitations recited in claim 26-30.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER